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INFLUENCE OF THEOBROMINE ON HEAT PRODUCTION AND BODY TEMPERATURES IN COLD-EXPOSED HUMANS: A PRELIMINARY REPORT

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ABSTRACT

One of the most successful class of drugs employed to enhance cold tolerance in animals appears to be the methylxanthines. Indeed, methylxanthines such as caffeine, theophylline and theobromine have been shown to increase heat production, delay hypothermia and thus improve cold tolerance in animals. In humans, theophylline and caffeine (taken in combination with ephedrine) have similarly been shown to improve cold tolerance. Whether theobromine could enhance tolerance to cold in humans, is not known. The influence of theobromine was thus investigated in eight healthy young male subjects during two semi-nude exposures to cold air (3h, 7°C, 1 m/s wind speed). The ingestion of theobromine (7.5 mg/kg at min 0; double-blind placebo-controlled trial) produced two different types of responses, as shown by a significant interaction between the effect of group (responders vs non-responders) and the effect of drug treatment (placebo vs theobromine) on the rate of decrease in mean body temperatures ($\overline{T}_b$). This interaction indicates that the effect of theobromine significantly changed as a function of the groups of subjects. Four subjects showed a significant reduction (or improvement) in the drop in $\overline{T}_{sk}$ and $\overline{T}_b$ with theobromine ingestion ($P<0.05$), whereas their core temperature (T_{re}) was not significantly affected by the drug treatment. These improvements were also associated with a 20% increase in heat production (not significant) and a 70% greater lipid oxidation ($P=0.08$). These 4 subjects were therefore considered as "responders" to the drug treatment. In addition, the other four subjects were considered as "non-responders", since their drop in $\overline{T}_{sk}$, drop in $\overline{T}_b$ and heat production remained unchanged by the ingestion of theobromine. However, their drop in T_{re} following the ingestion of theobromine was not smaller, but significantly greater than with the placebo ingestion (51%, $P<0.05$). The main difference between "responders" and "non-responders" in their placebo responses to the cold appeared to be the 25% lower

heat production and the corresponding 52% greater T_{re} cooling rate of the non-responders compared to the responders. In conclusion, the present results are interpreted as indicating that the ingestion of theobromine in subjects capable of producing a relatively high metabolic response to the cold, significantly improves cold tolerance by increasing heat production, mainly from a greater lipid utilization. Although theobromine did not significantly alter tolerance to cold in subjects with a relatively low metabolic response to cold, it significantly worsened their rate of T_{re} cooling, a side effect which certainly suggests that theobromine should be used in the cold with caution. Future work must be carried out to optimize the beneficial influence of theobromine and to minimize its side effect in cold-exposed humans.

KEYWORDS: core temperature, carbohydrate, cold air, energy substrates, heat production, heat losses, hypothermia, lipid, metabolism, oxygen consumption, protein, skin temperature.

INTRODUCTION

Environmental physiologists have been interested for many years in ergogenic aids to delay hypothermia and thus enhance tolerance to cold (5, 18). There are basically two approaches to delay hypothermia. The first one involves drugs that decrease heat loss without changing heat production. They will tend to lower skin temperatures, decrease manual dexterity and increase the danger of frostbite, but will only maintain core temperature if the cold challenge is not overwhelming. The second approach involves agents that elevate heat production. They would provide warmer core temperature (T_{re}), mean skin temperature ($\overline{T}_{sk}$), and thus enhance cold tolerance, as long as energy substrates are not limiting for thermogenesis, such as in prolonged starvation (16). The approach based on an increased thermogenesis appears a much more practical method.

Methylxanthines are definitely one of the most successful class of drugs used to improve tolerance to cold. In animals, caffeine, theophylline and theobromine, three well-known naturally-occurring methylxanthines have been shown to increase heat production in the cold, and consequently, delay hypothermia and ameliorate tolerance to cold (6, 18, 21). Similarly in humans, theophylline and caffeine (the latter in combination with ephedrine) have also been shown effective in improving cold tolerance (16, 19, 20). Whether theobromine ingestion in man could achieve the same result is not known. Since theobromine is found in common food items of the North-American diet (cocoa and chocolate), and since it is thought to produce the same metabolic effects as caffeine or theophylline, but without the central nervous system side effects (12), the utilization of theobromine could be quite beneficial to cold-exposed humans.

The purpose of the present study was to test the hypothesis that the acute ingestion of theobromine increases thermogenesis in the cold and improves cold tolerance by delaying hypothermia. It was thus hypothesized that such an enhanced tolerance to cold would be manifested by warmer body temperatures in the cold in comparison to a placebo. To verify this hypothesis, T_{re}, $\overline{T}_{sk}$ and mean body temperature ($\overline{T}_b$) were measured. In addition, oxygen consumption, energy expenditure and substrate utilization were all determined in an effort to elucidate the underlying mechanism of action.

METHODS

Subjects

Eight healthy young male volunteers participated in the present study. Each was examined by a physician who approved their participation in the study. The nature, purpose and possible risks of the study were carefully explained to each subject before he gave his written consent to participate. All subjects were allowed to withdraw from the study at any time without bias. In addition, subjects were withdrawn from the cold when their T_{re} went below 35.5°C. This protocol was reviewed and approved by the institutional human ethics committee. Subjects were given the opportunity to familiarize themselves with the protocol, including a 1 h cold air exposure. Some standard physical characteristics including body fat content (hydrostatic weighing) and maximal aerobic power ($\dot{V}O_{2max}$; Bruce protocol) were also determined.

Experimental Protocol

Two cold exposure tests (3h at 7°C; wind speed 1 m/s) were performed a week apart on each subject wearing only a bathing suit or jogging shorts. Subjects fasted for 12-14 h prior to the test, refrained from alcohol for at least 48 h before, and refrained from

exercise for 24 h before the test. All subjects were instrumented early in the morning with a rectal probe (Sherigan, Argyle NY), ECG leads and 12 heat flux transducers (Thermonetics, San Diego CA). The subjects then rested (sitting at 25°C) for 0.5 h before entering the cold room. One test was held following ingestion of a placebo capsule (cellulose) and another following the ingestion of a capsule containing theobromine (7.5 mg/kg U.S.P. grade, Wiler Chemicals London Ont.). The drug or placebo capsule was ingested immediately before entering the cold chamber, at time zero. Preliminary tests have revealed that a dose of 2 mg/kg of theobromine is without noticeable effect on cold tolerance, a dose between 5-10 mg/kg appeared as an optimal dose, whereas a dose of 20 mg/kg offered lesser improvements in body temperatures. Therefore, a dose of 7.5 mg/kg was used in the present studies. Four subjects received the placebo treatment first and drug treatment last, whereas four subjects received the drug first and placebo last. Both treatments were separated by at least one week and followed a double-blind placebo-controlled design.

Thermal Measurements

T_{re} was monitored using a thin thermistor probe inserted 12 cm beyond the anus. Skin temperatures and heat flux were measured with heat flow transducers using a 12 point system. $\overline{T}_{sk}$ was calculated by the following formula (8):

$$\overline{T}_{sk} = .07T(\text{head}) + .085T(\text{chest}) + .065T(\text{calf}) + .085T(\text{abdomen}) + .14T(\text{lower arm}) + .05T(\text{wrist}) + .095T(\text{front thigh}) + .065T(\text{shin}) + .07T(\text{foot}) + .09T(\text{upper back}) + .09T(\text{lower back}) + .095T(\text{rear thigh}). \quad \text{(eq. 1)}.$$

Mean heat loss was calculated from the heat flux measurements using the same weighting

factors as above (8, 16). $\overline{T}_b$ was calculated as 0.67 T_{re} + 0.33 $\overline{T}_{sk}$ (7, 14). All thermal data were continuously recorded with a data acquisition system (Hewlett-Packard 3497A and 236 Computer), as described elsewhere (17).

Respiratory Gas Exchange Measurements

Oxygen consumption and carbon dioxide production (converted to STPD values) were measured during the last 20 min of every 0.5 h interval of the 3 h cold exposure (Jaeger Ergo Oxyscreen Metabolic Cart, Wurzburg FRG). Values were interpolated during the short periods when the data were not being collected. Analyzers were checked for proper calibration before and at hourly intervals during the test. Indirect calorimetry was used to estimate heat production from the oxygen consumption, carbon dioxide production and the urinary urea nitrogen excretion (1, 2, 10, 13, 15). Non-protein respiratory exchange ratio (NPRER) was calculated from calorimetric data and urinary urea nitrogen excretion (Sigma Chemicals St Louis MO) during the test period. The quantity of urinary nitrogen excreted during the test period is an index of protein oxidation (1, 10, 13, 15). The oxidation of carbohydrate and fat were assessed by the amount of oxygen consumed per gram of substrate oxidized and by the NPRER for which, according to the tables of Lusk, a NPRER of 1.000 and 0.707 represents 100% carbohydrate and 100% lipid oxidation, respectively (13). The following calculations have been previously tested and validated, and were performed exactly as previously described (1, 2, 10, 13, 15).

$$CHO = (NPRER - 0.707) \bullet 0.293^{-1} \qquad \text{(eq.2);}$$

$$\text{Carbohydrate Oxidation } (g \bullet h^{-1}) = CHO \bullet \dot{V}O_{2np} \bullet 0.829^{-1} \qquad \text{(eq. 3);}$$

Fat Oxidation ($g \bullet h^{-1}$) = $(1 - CHO) \bullet \dot{V}O_{2np} \bullet 2.0193^{-1}$ (eq. 4);

Protein Oxidation ($g \bullet h^{-1}$) = urea nitrogen x 6.25 (eq. 5);

Metabolic Rate ($kJ \bullet h^{-1}$) = $(19.61 + CHO \bullet 0.361) \bullet \dot{V}O_{2np} + (18.66 \bullet \dot{V}O_{2prot})$ (eq. 6);

In the above equations, CHO is the term representing the ratio of carbohydrate over nonprotein oxidation; $\dot{V}O_{2np}$ and $\dot{V}O_{2prot}$ are the average nonprotein and the average protein oxygen consumption respectively ($L \bullet h^{-1}$); NPRER is the average nonprotein respiratory exchange ratio during the test period; 0.293 is the difference between a NPRER of 1 and 0.707; 0.829 and 2.0193 are the oxygen consumptions (litres) required for the oxidation of one gram of starch and one gram of triglyceride, respectively; 6.25 is the conversion factor for urea nitrogen to protein; 19.61 and 18.66 are the energy equivalent ($kJ \bullet L^{-1}$ oxygen) when lipid and protein only are oxidized respectively; 0.361 is the difference between the caloric equivalents of 1 litre of oxygen at a NPRER of 1 and 0.707 (1, 2, 10, 13, 15).

Heat Balance and Skin Conductance

Using the heat balance equation, the average heat debt was calculated as the difference between the average heat production and the average heat losses, as follows (3):

$$\dot{S} (W \bullet m^{-2}) = \dot{M} - [(\dot{R} + \dot{C}) + (\dot{E} + \dot{C})_{resp} + \dot{E}_{persp}] \text{ (eq.7);}$$

where $\dot{M}$ is the metabolic rate, $(\dot{R} + \dot{C})$ represent dry heat losses, estimated by the average mean heat flow of the 12 heat flux transducers (data not shown), $(\dot{E} + \dot{C})_{resp}$ are the convective and evaporative heat losses by the respiratory tract (8% of $\dot{M}$) (3) and

$\dot{E}_{persp}$ is the heat losses by cutaneous perspiration (taken as 4.1 $W \bullet m^{-2}$) (4). The mean level of skin conductance was estimated by the formula:

$$K_b\ (W \bullet m^{-2} \bullet °C) = (\dot{R} + \dot{C}) \bullet (T_{re} - \overline{T}_{sk})^{-1} \quad \text{(eq. 8);}$$

where T_{re} and $\overline{T}_{sk}$ are the average values during the cold test (data not shown) as described by Bittel (3).

Statistics

The main effects of group (responders vs non-responders; see Results) and drug treatment (placebo vs theobromine) as well as the possible interactions of treatments were assessed by a two-way analysis of variance, with repeated measures on the drug treatment (Biomedical Computer Programs, BMDP-85, Los Angeles, CA). Significant differences for the effect of theobromine within the same group of subjects were located using a two-tailed paired t-test. Furthermore, statistical differences between groups in the theobromine test, or placebo test, were appraised separately with two-tailed unpaired t-tests. Results are expressed as mean ± SEM.

RESULTS

Two entirely different types of responses to theobromine were observed in the cold. Indeed, four (4) subjects (SLL, ALV, MJD, DBB) showed a marked improvement in cold tolerance, as defined by a reduction in $\overline{T}_b$ cooling rate, whereas the four (4) others (TMM, KSG, BSS and JPP) showed no such improvement (Table 1). This was confirmed by the observation of a significant interaction between the effect of group and the effect of drug treatment on the rate of decrease in $\overline{T}_b$ ($P<0.01$), which indicated that the effect of theobromine changed significantly as a function of the group of subjects. Since the

thermal and metabolic responses of these 2 groups of "responders" (n=4) and "non-responders" (n=4) differed so much, a separate analysis was required, which is described below. Even though several important statistically significant differences were found, the analysis that follows will be of a descriptive nature, considering the limited number of subjects in each group. It should also be mentioned that the subject characteristics of these two groups of young healthy subjects are very similar (Table 2). Caffeine consumption of responders (117±102 mg/day) was similar to that of non-responders (170±136 mg/day).

Thermal Responses

Time spent in the cold (tolerance time) was unchanged by the ingestion of theobromine in "responders" and remained at 3h. *In "non-responders", it* was slightly reduced from 2.91±0.09 to 2.78±0.21 h by the ingestion of theobromine (non significant). Tolerance time of non-responders was less than the 3 h target because one subject was pulled out before the 3 h in the cold in both trials, when his T_{re} reached 35.5°C. Theobromine ingestion in responders did not significantly alter the rate of T_{re} decrease compared to their placebo trial (Fig. 1). That same parameter was not reduced, but significantly increased by 51% in non-responders ($P<0.05$; Fig. 1). It should also be mentioned that the rate of T_{re} cooling was 52% greater in the placebo trial of the non-responders compared to responders (Fig. 1). In addition to a significant interaction of treatments, the data were also affected by a significant main effect of group, which indicated that the the rate of $\overline{T}_{sk}$ decrease was significantly lower in responders, whatever the drug treatment ($P<0.05$). Theobromine ingestion reduced the rate of $\overline{T}_{sk}$ decrease by 16.5% in responders ($P<0.05$), whereas it was slightly increased in non-responders (Fig. 2).

Therefore, theobromine ingestion produced a significantly higher rate of $\overline{T}_{sk}$ decrease in non-responders than in responders ($P<0.05$; Fig. 2). The average $\overline{T}_{sk}$ maintained throughout the cold test tended to be warmer with theobromine in both responders (24.3±0.4 vs 25.0±0.5°C) and non-responders (23.3±0.2 vs 23.6±0.4°C). As with the $\overline{T}_{sk}$, the rate of $\overline{T}_b$ decrease was affected by a main effect of group ($P<0.05$). Indeed, theobromine ingestion in responders reduced the rate of $\overline{T}_b$ decrease by 16.6% ($P<0.05$), whereas it was slightly increased in the non-responders (Fig. 3). Therefore, theobromine ingestion produced a significantly higher rate of $\overline{T}_b$ decrease in non-responders than in responders ($P<0.05$; Fig. 3). The average heat debt was 46.6% lower after the ingestion of theobromine in responders (28.9±13.9 $W \bullet m^{-2}$), although it did not reach significance compared to the placebo (54.2±9.5 $W \bullet m^{-2}$). Average heat debt in non-responders was not changed by the drug treatment (67.3±7.5 $W \bullet m^{-2}$) compared to the placebo (72.4±16.7 $W \bullet m^{-2}$). Although non significant, skin conductance tended to be higher after theobromine ingestion not only in responders (13.4±0.5 vs 14.2±0.6 $W \bullet m^{-2} \bullet °C$) but in non-responders as well (12.1±0.6 vs 12.5±0.7 $W \bullet m^{-2} \bullet °C$).

Metabolic Responses

The rate of oxygen consumption tended to be higher in responders than in non-responders, whatever the drug treatment ($P=0.07$). As an example, the rate of oxygen consumption in the placebo test was 24.1% higher in responders than in the non-responders (n.s., Fig. 4). This difference was also observed when the oxygen consumption data was expressed per unit of body surface area (Fig. 4). In addition, it is equally important to note that theobromine ingestion in responders increased the rate of oxygen consumption by 21% compared to their placebo test (n.s., Fig.4). In contrast, the

rate of oxygen consumption was unchanged by the drug ingestion in non-responders, and it was significantly lower than the one with theobromine in responders ($P<0.05$; Fig. 4). Urinary urea nitrogen output was similar between the two groups and remained unaffected by the drug treatment (data not shown). NPRER was slightly lower with theobromine in responders, whereas it was unchanged in non-responders (Fig. 5). Energy expenditure tended to be higher in responders, whatever the drug treatment ($P=0.06$). Indeed, theobromine ingestion in responders increased energy expenditure by 20% (n.s.) whereas, theobromine ingestion in non-responders did not alter this parameter (Fig. 6). Similar to the oxygen consumption data above, energy expenditure from the placebo test of responders was 25% higher than in the placebo test of non-responders (n.s., Fig. 6). Similar results were found even when energy expenditure was expressed as a function of the body surface area (Fig. 6). Theobromine ingestion also increased the energy expenditure to a significantly higher level in responders than in non-responders ($P<0.05$, Fig. 6). As expected, theobromine ingestion in non-responders did not increase fuel metabolism, whereas in contrast, fuel metabolism was greatly influenced in the subgroup of responders. Indeed, lipid oxidation was increased by 70.6% ($P=0.08$), whereas carbohydrate or protein oxidation remained unchanged (Fig. 7). Carbohydrate oxidation was significantly lower in non-responders than in responders, whatever the drug treatment ($P<0.05$). Carbohydrate oxidation was significantly lower in the placebo test of non-responders than that of responsers ($P<0.05$, Fig. 7).

DISCUSSION

The results of this study demonstrate that the ingestion of theobromine in cold-exposed males produces two distinct types of physiological responses (Table 1). The observation of a significant interaction of treatments on the rates of $\overline{T}_b$ drop, clearly indicated that the effect of theobromine significantly changed as a function of the groups. Indeed the rate of $\overline{T}_b$ decrease was significantly reduced with theobromine in responders, whereas it was unchanged in non-responders (Fig. 3). In addition, $\overline{T}_{sk}$, heat debt and heat production of non-responders were unchanged by theobromine (Figures 2, 6, Results). However, their rate of T_{re} decrease was significantly increased with the drug treatment (Fig. 1). In marked contrast, the responders to the drug treatment showed significant improvements in their rate of $\overline{T}_{sk}$ cooling and no change in T_{re} (Figs. 1, 2), which were associated as expected, with a clear tendency for an increase in oxygen consumption and heat production (Figs. 4, 6). Evidently, the rate of $\overline{T}_{sk}$ drop was also influenced by a significant interaction of effect, meaning that the effect of theobromine changed as a function of the groups. It is important to emphasize at this point that the present theobromine-induced changes in body temperatures and oxygen consumption were caused by the drug treatment, and were not related to experimental error. This is supported by our previous demonstration that in similar cold exposure tests, the changes in T_{re}, $\overline{T}_{sk}$, $\overline{T}_b$ and average $\dot{V}O_2$ are highly reproducible (±3%) from one cold test to another in the same subjects (Vallerand, A.L. et al., unpublished manuscript). It must also be emphasized that the present changes in heat production, T_{re} and $\overline{T}_b$ in both responders (20%, 13% and 17% respectively) and non-responders (4%, -51% and -13% respectively) (Figs. 1, 3, 6) are of a similar magnitude as those previously published for the enhancement of cold

tolerance by ephedrine/caffeine (19%, 41% and 15% respectively) (16), theophylline during exercise (4%, 33% and 11% respectively) (20) and theophylline at rest (1%, 50% and 5% respectively) (19). These data also serve to illustrate how difficult it is to enhance maximal cold thermogenesis and cold tolerance in humans.

Mechanism of Action

The exact cellular mechanism by which theobromine improves cold tolerance is uncertain, but it appears related to an increase in heat production. With theobromine, heat production reached a higher level than the maximal cold-induced thermogenesis achieved in the placebo trial, leading to a supra-maximal cold thermogenesis (Fig. 6) (18). It is well-known that caffeine, theophylline and theobromine increase heat production in cold-exposed animals (6, 18, 21). The present data thus confirm the theobromine-induced increase in energy expenditure observed in animals and extend it to cold-exposed humans. In addition, previous studies have also shown that when a methylxanthine such as caffeine is ingested at comfortable ambient temperatures, its thermogenic effect depends on an increased utilization of lipid (2, 9). These observations would be in line with the present data showing that theobromine also selectively increased lipid oxidation (Fig. 7). In a recent publication, we have established that the ephedrine/caffeine induced improvement in heat production was dependent on an elevated carbohydrate oxidation (16). It is thus very interesting to observe that tolerance to cold can be improved not only by pharmacological agents that increase lipid oxidation (Fig. 7) but also by agents that increase carbohydrate oxidation (16). It has been documented that methylxanthines promote lipid mobilization, mainly through their antagonistic effect on cell surface adenosine receptors (2, 9, 12). Therefore the substrate mobilization/utilization effect of

theobromine (Fig. 7) during a physiological condition of increased energy demand such as cold exposure, would lead to an increase in lipid oxidation and consequently a greater production of heat and warmer body temperatures. It is well documented that increasing the oxidation of any substrate necessarily elevates the rate of heat production (11, 16).

Differences Between Responders and Non-Responders

Entirely different results were observed following the ingestion of theobromine in non-responders. Instead of improving cold tolerance, theobromine in non-responders had no influence on $\overline{T}_{sk}$, heat debt, heat production and fuel metabolism (Figs. 2, 3, 6, 7, Results). However, theobromine significantly increased the drop in T_{re} (Fig. 1). Therefore, we are not able to confirm our hypothesis that theobromine is beneficial in delaying hypothermia in all subjects. How can theobromine be beneficial to some subjects and detrimental (with respect to the drop in T_{re}) to others? The precise mechanism of action is not known, and is difficult to assess considering the present number of subjects. However, it may be related to a combination of two factors: peripheral vasodilation and heat production. A tendency for a slight increase in skin conductance was indeed observed following the ingestion of theobromine not only in responders but also in non-responders (see Results). This was probably related to the slightly warmer average $\overline{T}_{sk}$ encountered throughout the theobromine trial in all subjects (Results), suggesting a lesser vasoconstriction in the cold, or slight vasodilation, with theobromine in the cold (12). It is known that in responders, a warmer $\overline{T}_{sk}$ may also partly result from a greater heat production, whereas in non-responders, a slightly warmer $\overline{T}_{sk}$ could only be maintained at the expense of core temperature, since heat production was unchanged. Therefore it is suggested that theobromine ingestion produces in all

subjects a slight vasodilation as a side effect, which is devoid of consequences if heat production is simultaneously increased. However, if heat production is unchanged as in non-responders, the risk of hypothermia would be increased (Figs. 1, 6). This hypothesis nevertheless remains to be confirmed by blood flow measurements.

Another question that remains unanswered is why theobromine can increase heat production and fuel utilization in some subjects and not in others? One possible explanation is the sensitivity to methylxanthines. This seems unlikely since the daily consumption of caffeine was similar between the two groups of subjects, therefore tolerance or sensitivity to the effects of methylxanthines would not be different. Another possible explanation is that theobromine appears to increase heat production only in subjects with a relatively high metabolic response to the cold. Indeed, Figure 6 clearly shows that the average metabolic response to the placebo test (or cold-induced increase in heat production) was 25% higher in responders than in non-responders. It is possible that responders would benefit more from the increased lipid mobilization/utilization effect of theobromine than non-responders with a low metabolic response. This concept certainly deserves further investigation.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the present study has demonstrated that the ingestion of theobromine significantly improves cold tolerance in subjects capable of achieving a relatively high metabolic response to the cold. The present study has also shown that in contrast to responders, the ingestion of theobromine does not alter tolerance to cold of subjects with a relatively low metabolic response to the cold. These latter subjects suffered a significantly greater rate of drop in T_{re}, a side effect which suggests that theobromine should be used with caution in cold-exposed humans. It is recommended that further research be carried out to optimize the beneficial effects of theobromine, with a goal to extend the effects to subjects with a low metabolic response to the cold, and to clarify the optimal mode of administration that would maximize the beneficial effects associated with theobromine, without the side effects.

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TABLE 1: INDIVIDUAL RATES OF $\overline{T}_b$ DROP WITH THEOBROMINE.

	PLACEBO	THEOBROMINE	% CHANGE	DRUG RESPONSE
SLL	-1.17	-0.90	-22.9%	RESPONDER
ALV	-1.13	-1.03	-8.8%	RESPONDER
MJD	-0.97	0.70	-27.6%	RESPONDER
DBB	-1.13	-1.03	-8.8%	RESPONDER
TMM	-1.46	-1.64	+12.2%	NON-RESPONDER
KSG	-1.00	-1.13	+13.3%	NON-RESPONDER
BSS	-1.07	-1.40	+31.2%	NON-RESPONDER
JPP	-1.37	-1.37	0.0%	NON-RESPONDER

Rates of mean body temperature ($\overline{T}_b$) drop are in $°C \bullet h^{-1}$.

TABLE 2: SUBJECT CHARACTERISTICS OF RESPONDERS AND NON-RESPONDERS TO THEOBROMINE.

	RESPONDERS	NON-RESPONDERS
Age (y)	27.2±2.2	31.5±3.8
Height (m)	1.83± 0.04	1.77±0.03
Weight (kg)	77.0± 2.2	76.5±6.7
Surface area (m^2)	1.985± 0.047	1.928±0.089
VO_{2max} ($ml \cdot min^{-1} \cdot kg^{-1}$)	54.2± 2.1	49.1±1.4
Body fat (%)	13.2± 1.2	14.1±2.1

*: Results are expressed as mean±SEM of 4 subjects in each subgroup of responders (n=4) and non-responders (n=4).

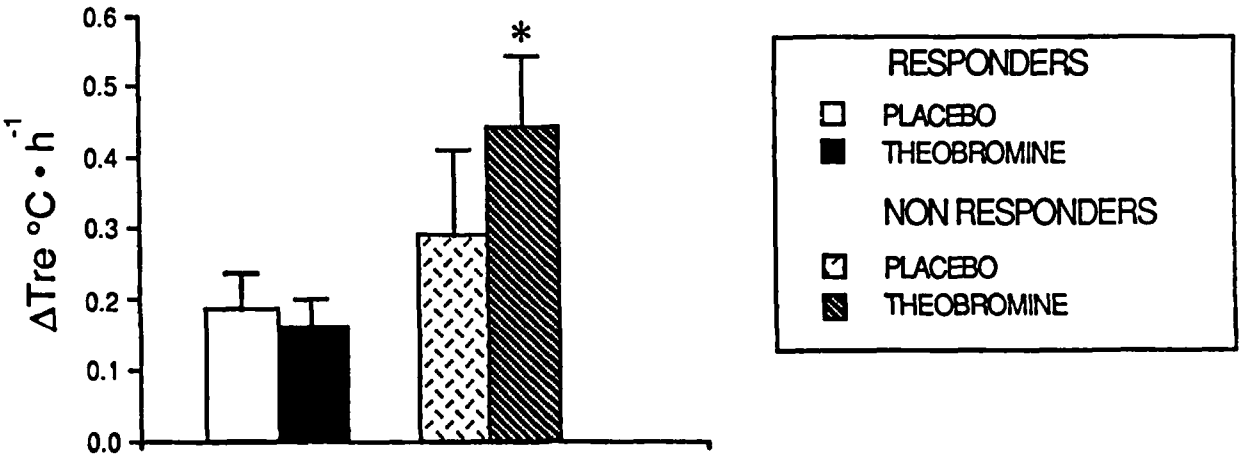

Figure 1. Rate of core temperature (T_{re}) decrease in the cold (7°C for target of 3h) following the ingestion of a placebo or theobromine (7.5 mg/kg at time 0) in responders and non-responders to the drug treatment. Results are expressed as mean ± SEM. Significant differences from the placebo condition are indicated by * ($P < 0.05$).

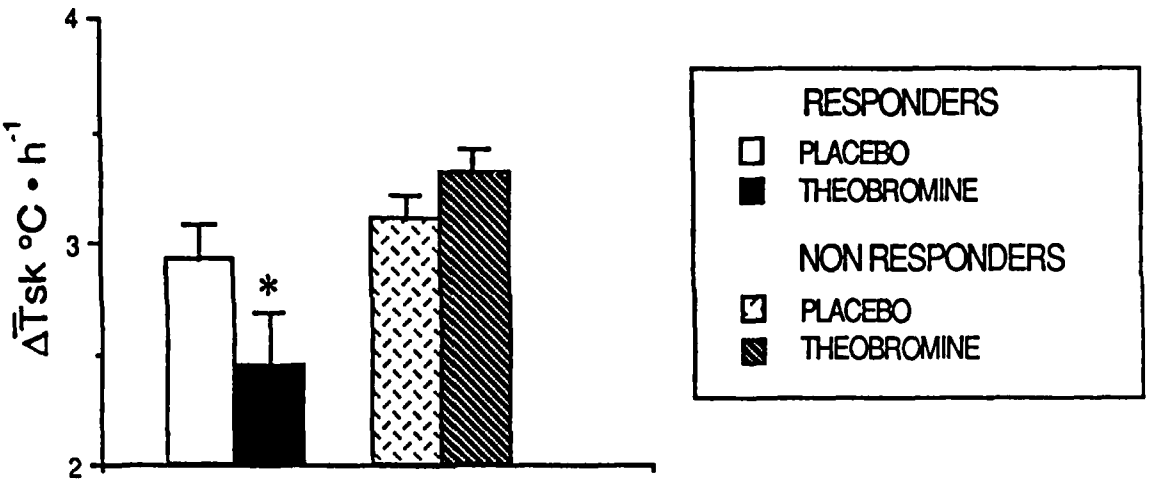

Figure 2. Rate of mean skin temperature (T_{sk}) decrease in the cold following the ingestion of a placebo or theobromine in responders and non-reponders (* = $P < 0.05$).

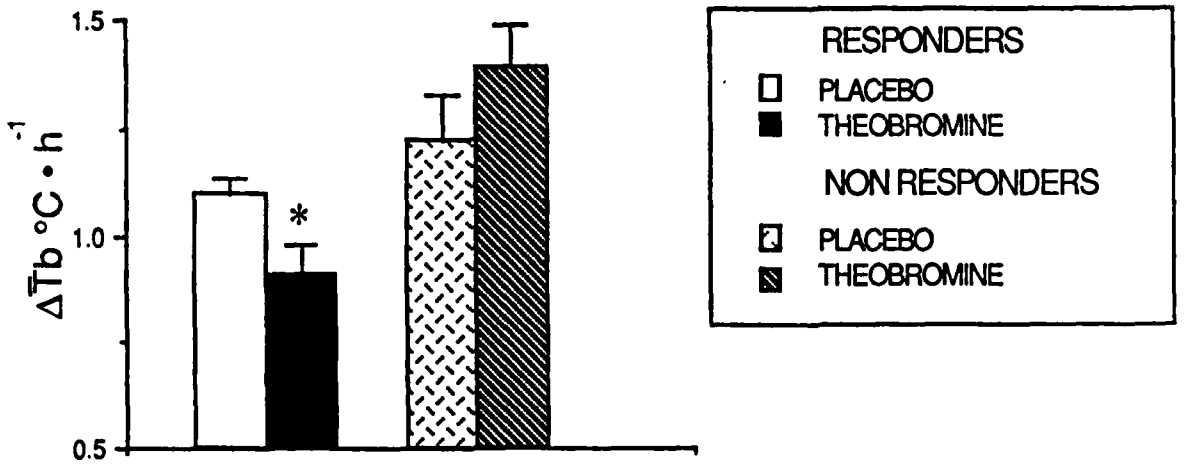

Figure 3. Rate of mean body temperature (T_b) decrease in the cold following the ingestion of a placebo or theobromine in responders and non-responders (* = $P < 0.05$).

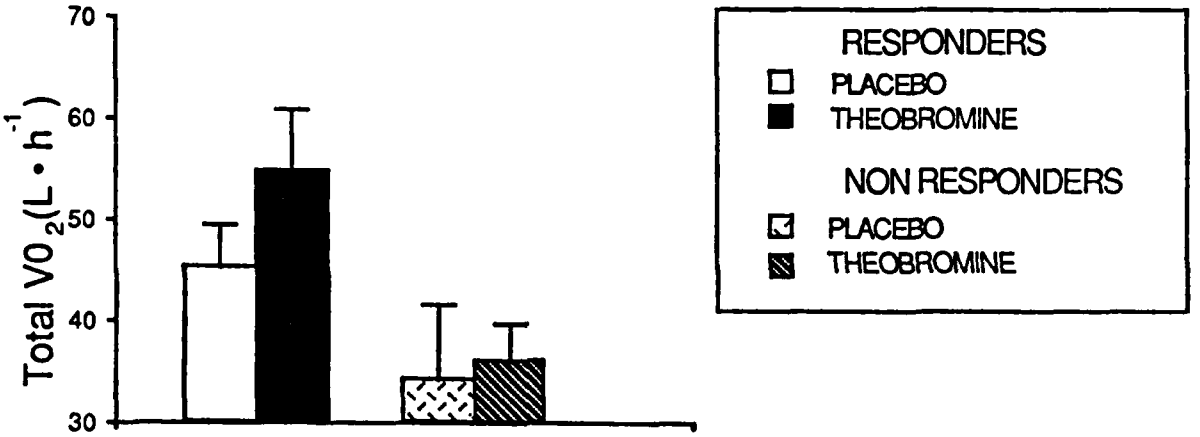

Figure 4. Average oxygen consumption (L/h STPD) in the cold following the ingestion of a placebo or theobromine in responders and non-responders. Oxygen consumption was measured during the last 20 min of each 0.5h of the 3 h test. Values were integrated and expressed per unit of time (hour).

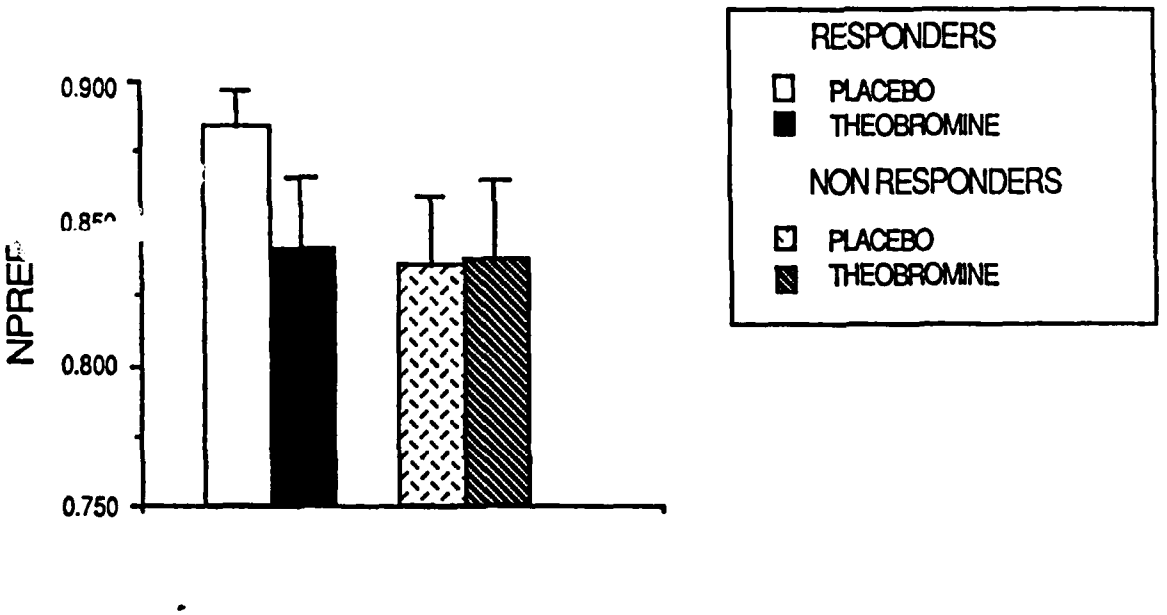

Figure 5. Average non-protein respiratory exchange ratio in the cold following the administration of a placebo or theobromine in responders and non-responders.

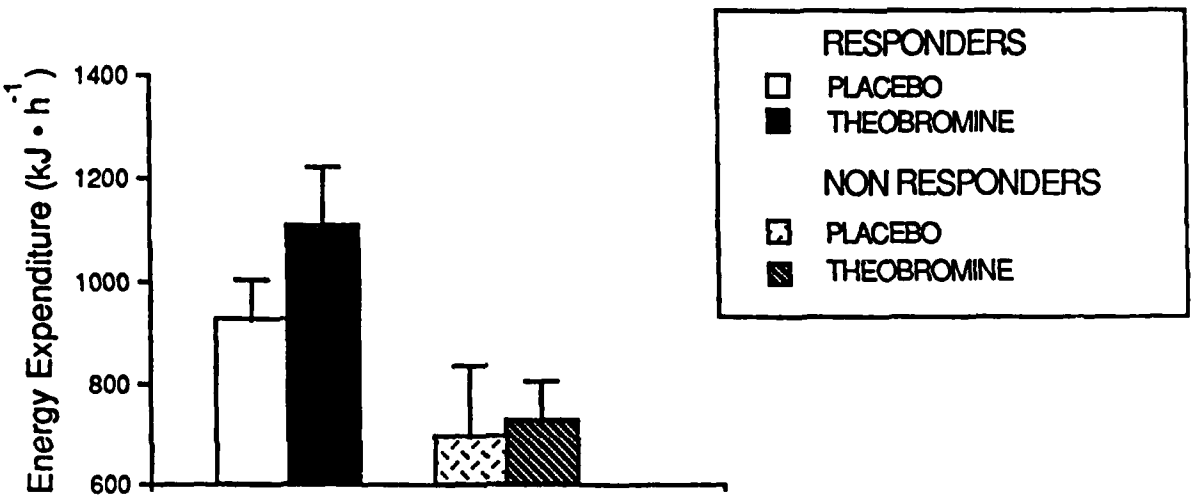

Figure 6. Average energy expenditure (kJ/h) in the cold following the ingestion of a placebo or theobromine in responders and non-responders.

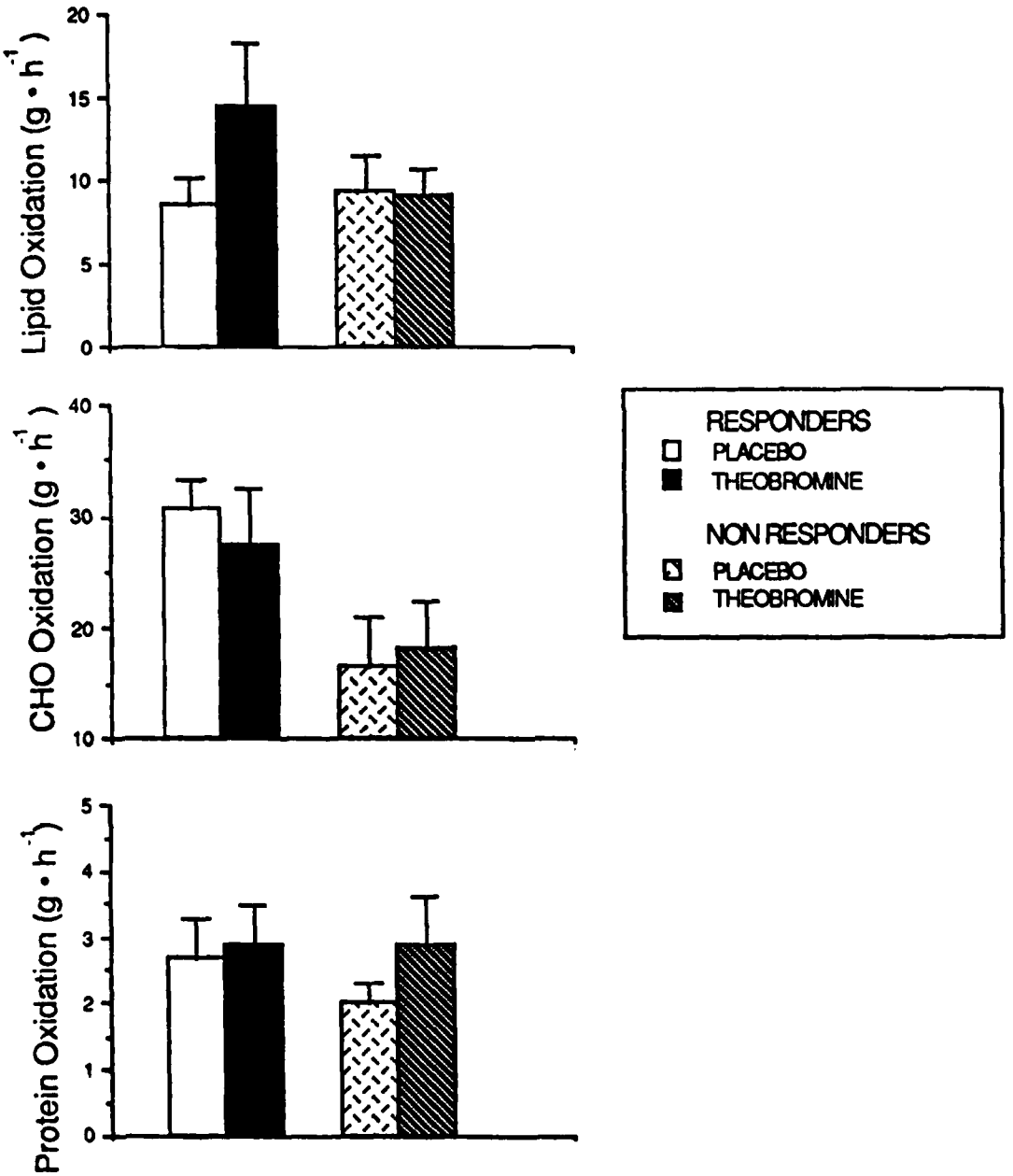

Figure 7. Rates of substrate oxidation in the cold following the ingestion of a placebo or theobromine in responders and non-responders. The utilization rates (g/h) of lipid, carbohydrates and protein are shown in the upper, middle and lower panels, respectively.

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One of the most successful class of drugs employed to enhance cold tolerance in animals appears to be the methylxanthines. Indeed, methylxanthines such as caffeine, theophylline and theobromine have been shown to increase heat production, delay hypothermia and thus improve cold tolerance in animals. In humans, theophylline and caffeine (taken in combination with ephedrine) have similarly been shown to improve cold tolerance. Whether theobromine could enhance tolerance to cold in humans, is not known. The influence of theobromine was thus investigated in eight healthy young male subjects during two semi-nude exposures to cold air (3h, 7°C, 1 m/s wind speed). The ingestion of theobromine (7.5 mg/kg at min 0; double-blind placebo-controlled trial) produced two different types of responses, as shown by a significant interaction between the effect of group (responders vs non-responders) and the effect of drug treatment (placebo vs theobromine) on the rate of decrease in mean body temperatures ($\overline{T}_b$). This interaction indicates that the effect of theobromine significantly changed as a function of the groups of subjects. Four subjects showed a significant reduction (or improvement) in the drop in $\overline{T}_{sk}$ and $\overline{T}_b$ with theobromine ingestion ($P<0.05$), whereas their core temperature (T_{re}) was not significantly affected by the drug treatment. These improvements were also associated with a 20% increase in heat production (not significant) and a 70% greater lipid oxidation ($P=0.08$). These 4 subjects were therefore considered as "responders" to the drug treatment. In addition, the other four subjects were considered as "non-responders", since their drop in $\overline{T}_{sk}$, drop in $\overline{T}_b$ and heat production remained unchanged by the ingestion of theobromine. However, their drop in T_{re} following the ingestion of theobromine was not smaller, but significantly greater than with the placebo ingestion (51%, $P<0.05$). The main difference between "responders" and "non-responders" in their placebo responses to the cold appeared to be the 25% lower heat production and the corresponding 52% greater T_{re} cooling rate of the non-responders compared to the responders. In conclusion, the present results are interpreted as indicating that the ingestion of theobromine in subjects capable of producing a relatively high metabolic response to the cold, significantly improves cold tolerance by increasing heat production, mainly from a greater lipid utilization. Although theobromine did not significantly alter tolerance to cold in subjects with a relatively low metabolic response to cold, it significantly worsened their rate of T_{re} cooling, a side effect which certainly suggests that theobromine should be used in the cold with caution. Future work must be carried out to optimize the beneficial influence of theobromine and to minimize its side effect in cold-exposed humans.

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KEYWORDS: core temperature, carbohydrate, cold air, energy substrates, heat production, heat losses, hypothermia, lipid, metabolism, oxygen consumption, protein, skin temperature.

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